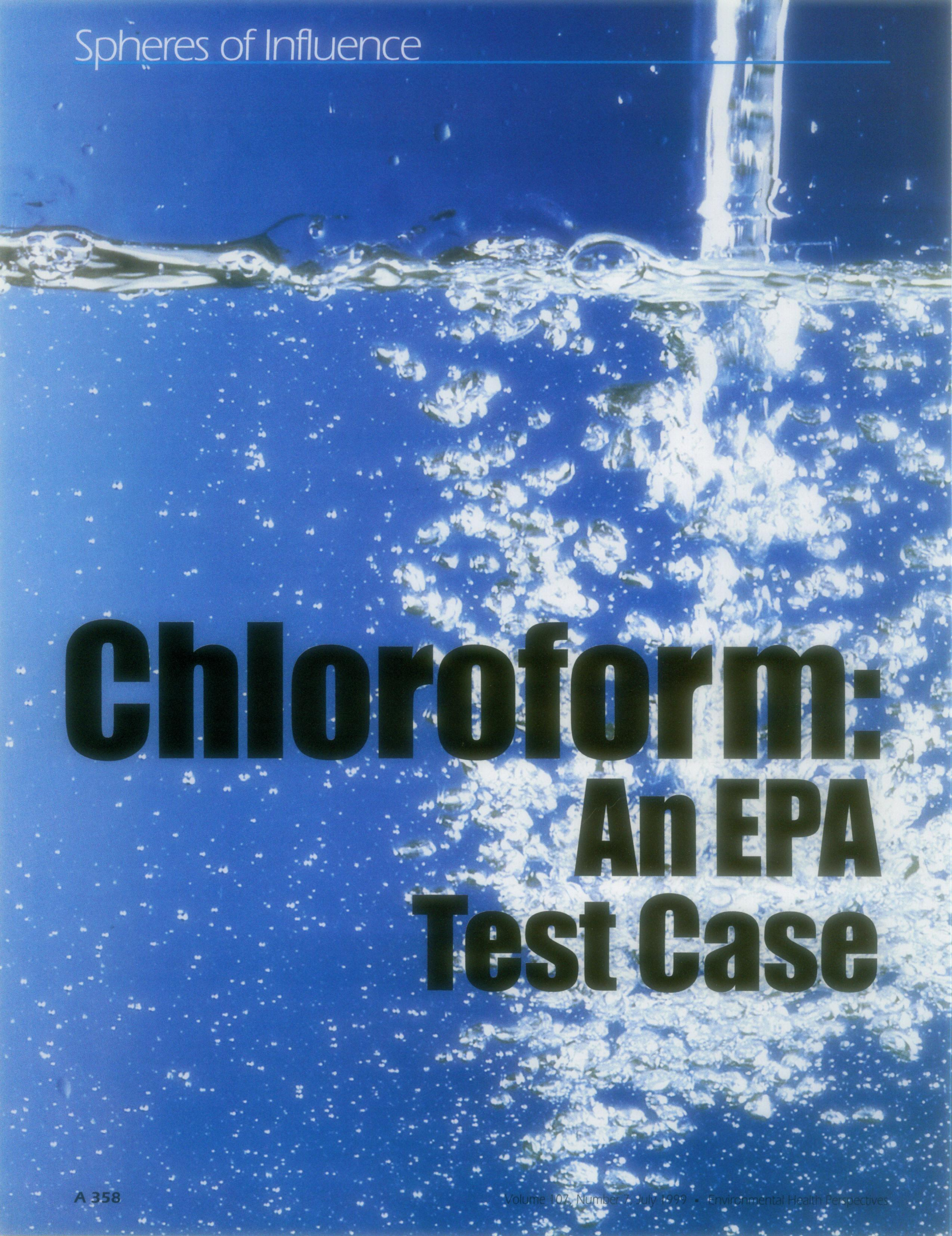

Chloroform: An EPA Test Case

On 31 March 1998, the U.S. Environmental Protection Agency (EPA) issued a Notice of Data Availability in the *Federal Register* to raise the drinking water maximum contaminant level goal (MCLG) for chloroform, a suspected human carcinogen, from zero to 300 parts per billion (ppb). MCLGs, which are required under the Safe Drinking Water Act (SDWA), are nonenforceable goal levels under which no adverse human health effects are expected. By contrast, maximum contaminant levels (MCLs) are enforceable standards that take issues of technical feasibility and compliance costs into account. MCLs are set as close to the MCLG as possible. By proposing to raise the MCLG, the EPA departed from its long-held default reliance on linear dose–response models, as prescribed by the agency's 1986 *Guidelines for Carcinogen Risk Assessment.* This document directed risk assessors to assume that any exposure to a chemical carcinogen, no matter how low, was associated with some degree of measurable cancer risk.

The EPA's more current thinking in this area is reflected in the *Proposed Guidelines for Carcinogen Risk Assessment,* the 1996 draft update to the 1986 guidelines. These new guidelines shift the focus of cancer risk assessment away from default assumptions on linearity toward an emphasis on mechanisms of action and a description of the conditions under which carcinogenic hazards are likely to be expressed. Under the new guidelines, the EPA is obligated to consider mechanistic data in the setting of regulatory goals and standards and, if warranted, to depart from assumptions of linearity in the setting of these regulatory values. As with the 1986 version, the 1996 guidelines were designed to advise risk assessors in both the laboratory and the field as to EPA policy regarding carcinogenic chemicals, and to provide guidance for those who advise decision makers and the public on the associated risks.

Chloroform appeared to be a good test candidate upon which the EPA could try out its new cancer risk assessment policies. An emerging body of evidence suggested that chloroform could produce tumors in animals only if the exposures exceeded a critical threshold dose preceded by obvious signs of toxicity. Based on these findings, some scientists suggested that chloroform was a nonlinear threshold carcinogen, meaning that there might be a level below which a person could be exposed to chloroform without the threat of cancer. But because the 1986 guidelines provided minimal guidance on how to use nonlinear dose–response data in the risk characterization process, efforts to revise regulatory policies for chloroform (or any other carcinogen, for that matter) based on mechanistic data were essentially stalled. With the release of the draft 1996 guidelines, proponents of a revised regulatory strategy for chloroform perceived a window of opportunity. By proposing to raise the MCLG for chloroform to 300 ppb, the EPA was opening a dialogue among stakeholders and possibly setting a precedent for the future evaluation of chemical carcinogens based on mechanistic data.

But the dialogue that ensued proved highly contentious. As news of the proposal spread throughout the public health and environmental community, scientists and advocates immediately issued an appeal to the EPA, claiming that chloroform's status as a threshold carcinogen in humans remained uncertain and demanding that the agency retain the existing health goal. To provide a forum on the issue, the EPA's Office of Water hosted a workshop in June 1998 in Washington, DC, and invited stakeholders to attend. The sharp nature of the disagreement among scientists on both sides of the issue was soon apparent; later in the year, the agency decided to drop the proposal from its final disinfectants and disinfection by-products (DBPs) rule for drinking water (which was issued on 16 December 1998), pending additional review.

The decision to abandon the revised goal and retain a linear approach led to a concerted lobbying and letter-writing campaign among industry representatives hoping for congressional support, and industry accusations that the EPA had succumbed to political pressure. That same month, a coalition comprising the Chlorine Chemistry Council and the Chemical Manufacturers Association (two industry trade organizations based in Arlington, Virginia) and a group of 11 water utility companies sued the EPA, claiming the agency had violated provisions of the SDWA by failing to set the standard for chloroform using the best available science. Two public interest groups, the Natural Resources Defense Council and Physicians for Social Responsibility, have since intervened in the lawsuit.

How the chloroform debate plays out is seen as a critical issue that will define policy under both the draft cancer guidelines and the SDWA. For these reasons, it is being watched closely by major research and policy organizations and high-level government officials, even at the level of Vice President Al Gore's office. According to Jeanette Wiltse, director of the Health and Ecological Criteria Division in the Office of Science and Technology in the Office of Water, the EPA Science Advisory Board will begin reviewing the chloroform risk assessment this summer. Pending the results of that evaluation, a revised MCLG for chloroform may yet see the light of day. Says Wiltse, "Chloroform is a stalking-horse for how we're going to do cancer risk assessment. Everything has come down to arguing about chloroform, but to me the real debate is how we're going to deal with new evidence about how carcinogens cause their effects."

Disagreements over Data

The proposed MCLG was based on a 1997 EPA- and industry-sponsored study titled *An Evaluation of EPA's Proposed Guidelines for Carcinogen Risk Assessment Using Chloroform and Dichloroacetate as Case Studies: Report of an Expert Panel,* which was conducted by the International Life Sciences Institute (ILSI), an international nonprofit research institute based in Washington, DC. The ILSI panel comprised 10 expert scientists from academia, industry, and government, and was chaired by Melvin Anderson of ICF-Kaiser International. In addition to EPA support, a portion of ILSI's funding came from industry groups, including the Chlorine Chemistry Council. Following its review, ILSI concluded that chloroform is nongenotoxic (does not react with DNA) and that cytotoxicity and regenerative cell proliferation are obligatory precursors to chloroform-induced liver and kidney tumors in mice and rats. The EPA tentatively concurred and proposed basing the MCLG on the reference dose for liver toxicity under the assumption that protection against that noncarcinogenic outcome would automatically protect against cancer, which could only occur at a higher dose.

What neither the ILSI panel nor the EPA considered adequately, say opponents to the measure, are "literally dozens" of epidemiological studies suggesting that chloroform in drinking water causes cancer. Chloroform is one of a group of chlorination by-products in drinking water. Epidemiological studies of chloroform have been controversial because the chemical is always present in water supplies along with brominated compounds such as bromodichloromethane (BDCM) and chlorodibromomethane (CDBM), which are both suspected genotoxic carcinogens in animals. All three compounds are included in a group of drinking water contaminants collectively known as trihalomethanes (THMs), which are regulated by the EPA as

a group with a combined MCL of 100 ppb (an MCL of 80 ppb is on the books but is not enforceable until 2001). Given that BDCM has been shown to produce tumors in multiple organ systems in several animal models, it is regulated as a carcinogen by the EPA and has an MCLG of zero. The evidence for CDBM is less conclusive, however, and it is not regulated as a carcinogen. The EPA has assigned it an MCLG of 60 ppb.

Hundreds of other chemical compounds are also commonly found in drinking water, which also complicates findings. "Epidemiology has the advantage of studying people," says Rory B. Conolly, a senior scientist at the Chemical Industry Institute of Toxicology, a toxicology research organization based in Research Triangle Park, North Carolina. "The disadvantage is that there's no such thing as a cohort exposed exclusively to chloroform."

However, opponents to the measure are not to be deterred; they point to a number of studies they believe show convincing evidence that chloroform causes cancer. Among these are a 1992 meta-analysis by Robert D. Morris, an associate professor in the Department of Family Medicine and Community Health at the Tufts University Medical School in Boston, published in the July 1992 issue of the *American Journal of Public Health*, which found that 4,300 cases of bladder cancer and 10,000 total combined cancer cases could be attributed to chlorination by-products in drinking water. Opponents also point to a study published in the July 1997 issue of the *American Journal of Public Health* by Timothy Doyle, a researcher in the Division of Epidemiology at the School of Public Health at the University of Minnesota in Minneapolis. Doyle's study concluded that Iowa women living in areas supplied by municipal water systems containing higher concentrations of chloroform were at significant risk for both colon cancer and total combined cancers. Because chloroform concentrations in water tested in the study were rarely elevated beyond 100 ppb, Doyle was unable to quantify risks above that level. Ronald Melnick, a toxicologist with the NIEHS and a critic of the EPA's revised goal, asks, "When there's measurable risk at levels below 100 ppb, how can the EPA justify a goal of 300 ppb?"

The EPA counters that it reviewed both studies, along with many others, but remains unconvinced. "We did review the epidemiology data," says Wiltse, "but none of the analyses were more than suggestive, although there were some odds ratios that were greater than one." Moreover, she adds, "The studies were of disinfected water, which contains hundreds of chemicals, not chloroform alone. Chloroform was simply measured in the Doyle study as an indicator of disinfection." In the 31 March 1998 Notice of Data Availability, the EPA pointed out that some positive associations were beset by confounding variables such as smoking, and that results often conflicted with respect to specific sources of exposure. Furthermore, the EPA disagreed with the approach used by Morris, which produced only single numerical estimates of risk, and instead used a set of the most appropriate studies to conduct a distributional "population attributable risk" (PAR) analysis that predicted that between 1,100 and 9,300 cases of bladder cancer might be associated with DBPs annually. PAR methodology, which presents a range of potential risks to populations rather than a single estimate, is often used by epidemiologists to provide a perspective on the potential magnitude of risks associated with various exposures. Critics of the PAR approach point to the conspicuous absence of any end points other than bladder cancer and add that despite the EPA's dismissal of the Morris data, its estimated range for annual bladder cancers captured the Morris study point estimate of 4,300 cases and its upper bound estimate of 9,000 approached the Morris estimate for all cancers combined. In other words, regardless of the differences in methodology, both studies arrived at essentially the same numerical estimate of the risk of bladder cancer from exposure to DBPs in drinking water. "So why all the sound and fury about the Morris study being unreliable?" asks Erik Olson, a senior attorney with the Natural Resources Defense Council.

Focus on Animal Studies

Proponents of a revised MCLG say the epidemiological associations should be viewed in light of toxicological evidence suggesting that cancer can be induced only with extremely high exposures that are often cytotoxic in target organs. Studies in several species of mice and rats support this view. In most cases, only concentrated, repeated doses, such as those produced by gavage, have proven effective. However, critics remain skeptical and suggest that chloroform carcinogenicity at doses below those causing cytotoxicity and regenerative cell proliferation isn't well characterized. Melnick, in particular, has found that low-dose exposures to brominated THMs including BDCM and DBCM can produce liver tumors in female mice with no effect on liver toxicity or hepatocyte proliferation. Whether chloroform is similarly capable, he says, is not certain, but he adds that there is cause for concern, given that chloroform and the brominated THMs all break down to the same genotoxic intermediate (phosgene).

Ironically, the proposal to set the MCLG for chloroform alone at 300 ppb is practically a moot point because the enforceable MCL for THMs as a group, including chloroform, is only 100 ppb. Because chloroform is seen as an indicator compound for drinking water THMs, actually detecting it at 300 ppb would mean that the MCL had been exceeded and that the water supply was in violation of the standard. But the goal of 300 ppb is especially desirable to drinking water suppliers, who see it as more readily achievable. Exactly how the EPA plans to reconcile the difference between the two standards remains uncertain.

George Lucier, director of the Environmental Toxicology Program at the NIEHS, says there's no doubt that the EPA will adopt a nonlinear approach for some carcinogens as it works its way through the 1996 cancer guidelines, which will likely be finalized this fall. "They may ultimately adopt such an approach for chloroform," he says. But Lucier concedes that chloroform studies have yielded some ambiguous data. "I think it was a close call," he says. "I can see how people would differ on which approach to use."

In any event, the whole issue is still an open book, and the value that the chloroform MCLG will ultimately be assigned remains to be seen. According to Wiltse, the original proposal of 300 ppb has already been abandoned as the EPA has begun considering additional source contributions for chloroform that include inhalational and dermal exposures. Incorporating these pathways into the risk equation has yielded revised estimates for the MCLG of between 60 and 70 ppb. Says Lucier, "This is a prototypical issue, more a matter of principle than of safe exposure levels. Industry would like to see the EPA implement the revised guidelines. It wouldn't take much more evidence to support a nonlinear approach for chloroform."

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